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Potential drug interactions in adults living in Manaus: a real-world comparison of two databases, 2019

Taís Freire Galvão[1], Tayanny Margarida Menezes Almeida Biase[2], Giulia Sartori Bruniéri[1], Marcus Tolentino Silva[3]
[1]School of Pharmaceutical Sciences, State University of Campinas, Campinas, Sao Paulo, Brazil
[2]Graduate Program of Pharmaceutical Sciences, Federal University of Amazonas, Manaus, Amazonas, Brazil
[3]Graduate Program of Pharmaceutical Sciences, University of Sorocaba, Sorocaba, Sao Paulo, Brazil

Corresponding Author Information
Taís Freire Galvão
taisgalvao@gmail.com
+55 (19) 3521-7149
https://orcid.org/0000-0003-2072-4834
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Abstract
Background: Software systems are commonly used by professionals to assist identification of drug interactions and to ensure the safe use of medications. Real-world evidence about the comparison of different drug interaction sources is scarce. *Objective:* To compare two drug interaction databases used to identify interactions in a population-based survey. *Methods:* This is a cross-sectional study based on a previous survey performed in the city of Manaus, Brazil, in 2019. We included adults aged 18 years and over who used two or more medicines 15 days prior to the interview. In order to assess potential drug interactions, we searched Micromedex and UpToDate databases. The primary outcome was the prevalence of potential drug interactions in each database. Weighted Kappa statistics was calculated to assess agreement on the presence of drug interaction, documentation and severity. *Results:* A total of 752 participants were included in the study. The prevalence of drug interactions was 43.8% (95% CI: 40.2, 47.3%) in UpToDate and 30.2% (95% CI: 26.9, 33.5%) in Micromedex. The agreement related to drug interactions between the two databases was fair (Kappa=0.631). For r severity (Kappa=0.398) and documentation (Kappa=0.311), the agreement was poor. *Conclusion:* Agreement among compared databases was sub-optimal. Better quality and transparency on evidence available in drug interaction sources are needed to support informed health care professionals' decision.
Keywords
Drug Interactions; Software; Documentation; Classification; Population Health

Introduction

A proper identification of drug interactions is essential to ensure the safety and effective use of medications.[1] Pharmacists play a significant role in guiding drug therapy and the rational use of medicines in different levels of health care.[2-4] Clinical decision support software systems are commonly used in hospitals and in the community to assist

pharmacists in identifying drug interactions of clinical significance.[5] These systems that are used by pharmacists and other health professionals to identify interactions have evolved to integrate computerized screening banks for drug interactions, clinical information, and other drug-related problems.[6-8]

Although this software tools can increase the ability of pharmacists to detect clinically significant interactions, these systems are far from fail-safe.[5, 9] Optimal clinical decision support software should have a balance between low and high-risk alerts.[10, 11] Excessive warnings can cause tiredness and suppression of clinically significant interactions, while the warning shortage can increase the risk of ignoring possible damage and decrease the user's perception in relation to the reliability and usefulness of the system.[12]

Searching for drug interaction is not a trivial step, as there is a wide variety of search sources, from package inserts to medicines, scientific literature and various databases and websites. This diversification of sources makes the search difficult when looking for reliable information about drug interactions and ensuring patients about receiving safe drug therapies. Assessments of software performance to identify potential drug interactions mainly focus on hospital environment or are based on theoretical scenarios[13-17], involving patients with multimorbidity, in polypharmacy and old age.[18] This highly selected population, usually from the hospital[19] may not reflect the reality of multiple drug use and possible interactions by the general population. A limited number of studies have investigated the prevalence of potential drug interactions in the general population. Further assessments comparisons of sources for assessing potential drug interactions in the community can add valuable information, especially in less developed settings.[18, 20] We aimed to compare two systems of drug interaction for a population-based survey.

Methods

Study design

This is a cross-sectional study based on a previous survey performed in the city of Manaus from April to June 2019.[21]

Setting

The study setting was Manaus, the city capital of the State of Amazonas, with an estimated population of 2,219,580 people in 2020.[22]

Participants who had taken two or more medications in the past 15 days were assessed for the presence of potential drug interactions.

Participants

The adults who were included in the study were those at the age of and over 18 years who self-reported using two or more medicines 15 days prior to the interview. In the original survey, the participants were selected by probabilistic sampling carried out in three stages: (1) design of the census tracks of the city, (2) systematic selection of households, and (3) design of the individual interviewed based on sex and age quotas.[21] The sample size was calculated as 2,300 participants for the main study – not restricted to individuals who took at least two medicines – considering 20% of healthcare usage, confidence level of 95%, absolute precision of 2%, design effect of 1.5, and 2,106,355 in habitants aged ≥18 years living in Manaus.[21] Based on the results obtained in present analysis, *pos-hoc* sample size was calculated.

Variables

The primary outcome was the prevalence of potential drug interactions. For clarity, in this study, we use drug interactions as a synonym of potential drug interaction. The independent variables were sex (men, women), age (in years, categorized as: 18-24, 25-34, 35-44, 45-59, ≥60), economic classification (A/B, C, D/E, according to the 2018 Brazilian economic classification criteria, in which A is the wealthiest and E is the

poorest class)[23], education (higher education or beyond, high school, elementary school, below elementary school), health status (good, fair, poor), chronic diseases (yes, no), number of drugs used in the last 15 days (2, 3-4, ≥5).

Data sources and measurement

Experienced interviewers visited the participants' households in this study. The interviews were georeferenced and the data collected were stored in electronic devices. In the research, the following question was also included: "*Have you taken any medications in the last 15 days (two weeks)?*", and its possible answers: "yes" or "no." If so, the name of the medication was registered as informed by the participant and could be confirmed checking the medication packages and/or available medical prescriptions. The data were archived in the Microsoft Excel® 2010 software and the drugs were coded according to the Brazilian Common Denomination and, subsequently, according to the World Health Organization's Anatomical Therapeutic Classification System (ATC). Ineligible drugs or without an ATC code were classified as "uncoded".[24] . From February to March 2021, we searched IBM Micromedex® Drug Interaction Checking[25] and Lexicomp® Drug Interaction from UpToDate®[26] to identify the drug interactions. These databases are commonly used to investigate drug interaction in clinical practice and subscription was available for research team, allowing present investigation.

All ATC-coded drugs were assessed in each database to verify drug interactions. If positive for drug interactions, the combination of drugs, severity and documentation was recorded according to the classification of the database used. Commercial combinations of drugs not available as association in the database were searched by including each substance separately and interaction was recorded if occurred between the association and the other medicine. Both databases classify drug interactions according to severity and documentation. Micromedex classifies severity of drug interactions as: contraindicated (medications are contraindicated for concomitant use), major (the interaction may be life-threatening and/or require medical intervention to reduce or avoid serious adverse effects), moderate (the interaction may result in the health problem exacerbation and/or require treatment change), and minor (the interaction would result in limited clinical effects).[25] In this database, documentation is categorized into: excellent (interaction confirmed from controlled studies), good (the interaction exists, but there is absence of properly controlled studies), and fair (the available documentation is unsatisfactory, but pharmacological considerations lead clinicians to suspect the existence of the interaction).

UpToDate database defines severity as: major (effects may result in death, hospitalization, permanent injury, or therapeutic failure), moderate (medical intervention needed to treat effects, effects do not meet criteria as major), and minor (effects would be considered tolerable in most cases, no need for medical intervention). Documentation reliability is defined as excellent, good, fair, and poor. It also assigns a risk rating, which is a rapid indicator regarding how to respond to the interaction: A (unknown interaction), B (minor, no action required), C (moderate, monitor therapy), D (main, consideration to modify therapy) or X (contraindicated, avoid combination).[26]

To allow comparability of the databases, 'contraindicated' severity category from Micromedex was regrouped in 'major'; 'poor' documentations from UpToDate were rated as 'fair'; and interactions of risk 'A' from UpToDate were disregarded (considered as no drug interaction).

Bias

The data was collected by a team of experienced and trained interviewers.[21] The participant could optionally present the medicine package mentioned in the interview to

confirm the data and avoid misclassifications. To ensure the encoding of all medicines according to the ATC, herbal and homeopathic products were not included in the research.

Statistical methods

Participants were described statistically according to independent variables. Frequency of drug interactions, severity and documentation classifications in each database were described, as well as more relevant disagreements on interactions between them (major severity or excellent documentation in one database was not considered as a drug interaction in the other).

Weighted Kappa statistics was calculated to assess agreement on drug interaction, documentation and severity classifications between both databases. Kappa values >0.75 were considered as excellent agreement beyond chance, between <0.75-0.40 represented fair agreement, and values <0.40 denoted poor agreement beyond chance.[27]

Ethics approval

This study was approved by the Ethics Committee of the Federal University of Amazonas (Opinion No. 3,102,942), on December 28, 2018 (Certificate of Presentation for Ethical Appreciation 04728918.0.0000.502020). All participants signed a term of free and informed consent.

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Results

From 2,321 interviewed, 752 participants were taking two or more medicines and were included in the study. Most participants were women (58.6%), aged 45-59 years (27.3%), economic classification C (low middle class, 54.5%), higher education (49.2%), self-reported good health status (49.7%), had chronic diseases (76.2%), and used only two drugs (49.3%; Table 1). The prevalence of drug interactions in UpToDate was 43.8% (95% CI: 40.2, 47.3%) and, in Micromedex, 30.2% (95% CI: 26.9, 33.5%).

A total of 344 unique participants were reported with the presence of drug interactions in one or in both databases. More patients had drug interactions according to UpToDate (n=329) Micromedex (n=227); and 212 patients with drug interactions were identified by both databases (Figure 1).

The agreement on drug interactions between the two databases was fair (Kappa=0.631). Using UpToDate, over half of interactions were classified as moderate severity (61.2%), while Micromedex classified most as major severity (62.6%). Between the databases, the agreement on severity classification was evaluated as poor with a Kappa value of 0.398. In both databases more than half of the interactions were based on fair documentation (UpToDate: 70.6%; Micromedex: 61.4%) and documentation agreement was poor (Kappa=0.311) (Table 2). The post-hoc minimum sample size based on this agreement would be 94 patients sample size.

Among the more relevant classification disagreements identified between the databases, 27 different discordant drug interactions were reported with major severity or with excellent documentation in one database and not detected in the other (Table 3). Out of these discrepant classifications, 20 were present only in UpToDate (n=13 with major severity, n=7 with excellent documentation), and seven present only in Micromedex (n=6 with major severity, n=1 with excellent documentation). Most frequent drug interactions showed in UpToDate were related to major severity interactions: carisoprodol-orphenadrine (n=10), chlorpheniramine-orphenadrine (n=8) and ciprofloxacin-ibuprofen (n=3); and in Micromedex, acetylsalicylic acid-hydrochlorothiazide (n=3). The paracetamol-tramadol interaction (n=3) presented excellent documentation and minor severity in UpToDate. All major severity drug

interactions were related to fair documentation, according to UpToDate and, based on Micromedex, the major severity interactions were fair (n=4) and good documentation (n=2). The drug interaction of excellent documentation (minor severity) was amitriptyline-estradiol (n=1), according to Micromedex and not present in UpToDate. Drug interactions with excellent documentation ranged from minor (n=7) to moderate (n=1) severities, in UpToDate and not present in Micromedex. Most major severity interactions in UpToDate belonged to X risk classification (9 of 13), and minor severity interactions were classified as B risk (6 of 7) (Data not shown in Tables).

In UpToDate, orphenadrine appeared in seven different drug interactions that were not similarly regarded in Micromedex. Moreover, it was the most frequent drug involved in these discordant interactions (Table 3). Nonsteroidal anti-inflammatory drugs (NSAIDs) were the main ones in drug interactions, present in nine different drug interactions, and additive effects between medicines were the main mechanism of the interactions (n=10).

Discussion

Drug interactions were present in 3 to 4 people among 10 adults living in Manaus, according to the consulted databases, showing a higher frequency in UpToDate than Micromedex. Agreement on the identification of drug interaction between the databases was considered fair, while severity and documentation classifications of these interactions had poor agreements. Depending on the source used, a lot of work may result from screening drug interaction in the population setting.

Due to the cross-sectional nature of this study, participants were not monitored over time to confirm the occurrence of adverse events due to drug interactions. Based on a list of self-reported medicines used by the participants 15 days before the interview, we assessed drug interactions and did not clinically investigate these interactions. This limitation can make our results prone to memory and information biases. The databases are periodically updated and may have undergone changes during or after the study, also potentially affecting our results.

In agreement with our findings, a higher prevalence of drug interactions was observed when UpToDate was the reference for interactions. In the United States, an assessment performed in 2012 by screening 240 patients' medication profiles showed almost twice as many drug interactions using Micromedex.[28] In Turkey, a study with 80 renal transplant recipients observed similar results, presenting almost twice drug interactions identified in UpToDate in comparison to Micromedex.[29] The use of different databases shows the lack of agreement on the amount of possible drug interactions in different investigations, including ours, which raises concerns about the clinical relevance of checking multiple sources. Excessive alerts in clinical practice can lead to high workload for health care professionals and mask important alerts.[30, 31]

Micromedex and UpToDate had a fair agreement on the identification of drug interactions. Similar result was observed in previous studies that investigated agreement on multiple sources of drug interactions in clinical practice, including drugs for metabolic disorders, antiretrovirals, antimicrobials, and psychiatric drugs.[13, 16, 32, 33] A study involving common therapeutic combinations of drugs for bipolar disorder tested 125 pairs of drug interactions in six databases in 2019, presenting low agreement among the databases assessed.[16] Assessment of drug interactions in an Indian hospital using Epocrates and Medscape presented a significant discrepancy between the severity categories of drug interactions in 2015.[34] A retrospective analysis in an intensive care unit in Germany, including prescriptions for transplant patients, used five databases to identify drug interactions and only 9% of interactions were identified by all of them, showing discrepancies in the overall performance of these tools.[35]

When comparing the documentation and the severity classifications, the agreements between Micromedex and UpToDate were poor. Based on Micromedex, the interactions identified were more frequently rated as major severity, whereas, based on UpToDate, they were more frequently rated as minor or moderate. Most drug interactions relied on fair documentation in both databases. The assessment of drug interactions involving 78 patients from an Australian hospital in 2018 was compared using three databases: Stockley's Drug Interactions, Micromedex and YouScript. The results were low agreement on the severity classification of the consulted interactions.[36] Cross-sectional systematic comparative study using drug pairs, conducted in the United Arab Emirates in 2020, identified disagreements on the severity and documentation of drug interactions between eight databases: Micromedex reported a greater number of interactions related to major severity when compared to other databases (Portable Electronic Physician Information Database, UpToDate, Medscape, Drugs.com, Stockley's Drug Interactions, Drug Interactions Analysis & Management: Facts and comparisons and British National Formulary).[37]

Most of the drugs involved in discordant drug interactions were over-the-counter, such as ibuprofen, diclofenac, paracetamol and dipyrone. Drugs for treatment of chronic diseases, such as hypertension, heart disease and diabetes were also frequent. Among the discordant drug interactions between the two databases analyzed, most were identified from UpToDate. More frequent management showed that simultaneous use should be avoided, and the potential result of the interactions consisted mainly of enhancing or decreasing therapeutic effects with mostly unknown mechanisms of action. Mostly, the alerts were based on minor severity and fair documentation promoting alerts that are not considered clinically relevant by the health team.

Health care professionals are under constant pressure to provide appropriate care by making clinical decisions on a daily basis, with the help of drug information databases. The choice of the database can impact patient care and its outcomes.[38] Such sources, usually provided on a subscription-basis, should be periodically reviewed to improve relevant information based on high quality evidence from real-world data. Investments on well-designed studies to determine the incidence, outcomes, and risk factors related to the patient affected by drug interactions are needed to support the provided recommendations. Algorithms to define systematic and clear evidence assessment processes to assess the risk and severity of drugs should ideally be integrated into these electronic systems.[39] This low quality of evidence potentially overestimates the severity of drug interactions and also leads to overriding warnings when they are considered less serious, which can gradually neglect the serious drug interactions.[33] These disagreements disadvantage health professionals when making clinical decisions in cases of drug interaction in which the patient's condition justifies the use of both drugs that interact with each other, especially when there are no alternatives available.[33, 37]

We also observed that the search for drugs available as commercial combinations may interfere with the result of drug interactions in the database, such as those including dipyrone and orphenadrine, commonly used combined in Brazil. Since these sources are based on developed settings, these fixed combinations are usually not included in the databases and may represent a higher burden in searching for interaction. Professionals should also be aware when searching for the active ingredients separately, for it is possible to find interactions between active ingredients contained in a combination.

Conclusion

As for the identification of drug interactions, slight agreement was observed between UpToDate and Micromedex in this real-world analysis, showing poor agreement on severity and documentation of drug interactions. Consulting multiple databases to identify drug interactions may increase health professionals' workload, as well as undetermined clinical outcomes for patients. Better-qualified sources for getting drug information are in need so that they can provide better support for health professionals and patients.

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Table 1. Main characteristics of participants taking two or more medicines (n=752)

Variables	n	%
Sex		
Male	311	41.4
Female	441	58.6
Age (years)		
18-24	108	14.4
25-34	168	22.3
35-44	147	19.6
45-59	205	27.3
≥60	124	16.5
Economic classification		
A/B	108	14.4
C	410	54.5
D/E	234	31.1
Education		
Higher education or beyond	60	8
High school	370	49.2
Elementary school	125	16.6
Below elementary school	197	26.2
Health status		
Good	374	49.7
Fair	292	38.8
Poor	86	11.4
Chronic diseases		
No	179	23.8
Yes	573	76.2
Number of medicines		
2	371	49.3
3-4	304	40.4
≥5	77	10.2

Fig. 1. Agreement of drug interactions between UpToDate and Micromedex

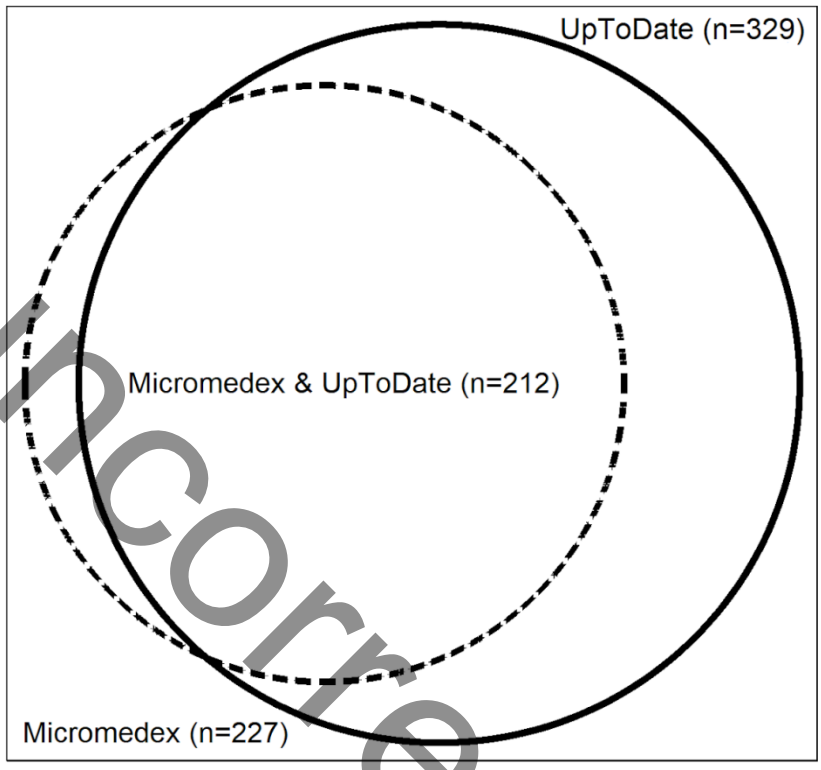

Table 2. Agreement of drug interaction between the databases

Variable	UpToDate		Micromedex		Kappa
	n	%	n	%	
Interaction[a]					0.631
No	423	56.3	525	69.8	
Yes	329	43.8	227	30.2	
Severity[b]					0.398
Minor	61	9.1	10	2.2	
Moderate	411	61.2	161	35.2	
Major	200	29.8	286	62.6	
Documentation[b]					0.311
Fair	473	70.6	282	61.4	
Good	169	24.93	87	19.4	
Excelent	30	4.48	88	19.2	

[a] n=752 patients

[b] n=672 interactions in UpToDate; n=457 interactions in Micromedex

Table 3. Characteristics of discordant drug interactions

Drug combination	N	Severity	Documentation	Management	Potential outcome	Mechanism	Database
Carisoprodol, orphenadrine	10	Major	Fair	Concurrent use should be avoided	CNS[a] depressants may enhance orphenadrine effects	Additive CNS[a] depression	UpToDate
Chlorpheniramine, orphenadrine	8	Major	Fair	Concurrent use should be avoided	CNS[a] depressants may enhance orphenadrine effects	Additive CNS[a] depression	UpToDate
Acetylsalicylic acid, hidrochlorothiazide	3	Major	Good	Monitor worsening renal function signs and assure diuretic efficacy	Reduced diuretic effectiveness and possible nephrotoxicity	Decreased production of renal prostaglandins	Micromedex
Ciprofloxacin, ibuprofen	3	Major	Fair	Consider the increased risk of seizure	Increased seizure-potentiating effect of quinolones	Enhanced central GABA-A[b] inhibition, increased epileptogenic potential of the quinolone	UpToDate
Paracetamol, tramadol	3	Minor	Excellent	No action required	Decreased paracetamol absorption	Impairment in gastric motility	UpToDate
Ciprofloxacin, dipyrone	2	Major	Fair	Consider the increased risk of seizure	Increased seizure-potentiating effect of quinolones	Enhanced central GABA-A[b] inhibition, increased epileptogenic potential of the quinolone	UpToDate
Loratadine, orphenadrine	2	Major	Fair	Concurrent use should be avoided	CNS[a] depressants may enhance orphenadrine effects	Additive CNS[a] depression	UpToDate
Scopolamine, orphenadrine	2	Major	Fair	Concurrent use should be avoided	CNS[a] depressants may enhance orphenadrine effects	Additive CNS[a] depression	UpToDate
Acebrophylline, caffeine	1	Major	Fair	Should not be coadministered	Enhanced stimulatory effect of CNS[a] stimulants	Not informed	UpToDate
Amitriptyline, orphenadrine	1	Major	Fair	Concurrent use should be avoided	CNS[a] depressants may enhance orphenadrine effects	Additive CNS depression	UpToDate

Drug combination	N	Severity	Documentation	Management	Potential outcome	Mechanism	Database
Amlodipine, calcium carbonate	1	Moderate	Excellent	Monitor decreased therapeutic effects	Decreased therapeutic effect of amlodipine	Not informed	UpToDate
Amlodipine, ibuprofen	1	Minor	Excellent	No action required	Decreased antihypertensive effect of amlodipine	Unknown	UpToDate
Budesonide, diclofenac	1	Major	Fair	Monitor bleeding signs	Increased risk of gastrointestinal ulcer or bleeding	Additive effects	Micromedex
Budesonide, dipyrone	1	Major	Fair	Monitor bleeding signs	Increased risk of gastrointestinal ulcer or bleeding	Additive effects	Micromedex
Budesonide, ibuprofen	1	Major	Fair	Monitor bleeding signs	Increased risk of gastrointestinal ulcer or bleeding	Additive effects	Micromedex
Bupropion, desvenlafaxine	1	Major	Fair	Low-dose starting treatment and gradually increase	Lower seizure threshold	Unknown	Micromedex
Calcium carbonate, gliclazide	1	Minor	Excellent	No action needed	Increased gliclazide absorption	Not informed	UpToDate
Carbamazepine, dipyrone	1	Major	Fair	Avoid concurrent use of dipyrone with myelosuppressive agent	Enhanced toxic effect of Myelosuppressive agents	Use of dipyrone is associated with a risk for agranulocytosis and pancytopenia but mechanism is unknown	UpToDate
Dexchlorpheniramine, orphenadrine	1	Major	Fair	Concurrent use should be avoided	CNS[a] depressants may enhance orphenadrine effects	Additive CNS[a] depression	UpToDate
Esomeprazole, omeprazole	1	Minor	Excellent	Standard clinical care measures	Increased serum concentration of omeprazole	Inhibition of CYP2C19 [c], responsible for omeprazole metabolism	UpToDate
Gliclazide,	1	Major	Fair	Consider a decrease in	Enhanced hypoglycemic	Not informed	UpToDate

Drug combination	N	Severity	Documentation	Management	Potential outcome	Mechanism	Database
vildagliptin				gliclazide dose and monitor patients for hypoglycemia	effect of gliclazide		
Lithium carbonate, promethazine	1	Major	Good	Monitor signs of toxicity or extrapyramidal symptoms	Weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy and brain damage	Unknown	Micromedex
Morphine, orphenadrine	1	Major	Fair	Concurrent use should be avoided	CNS[a] depressants may enhance orphenadrine effects	Additive CNS[a] depression	UpToDate
Morphine, paracetamol	1	Minor	Excellent	No action required	Decreased paracetamol absorption	Impairment in gastric motility	UpToDate
Naproxen, nifedipine	1	Minor	Excellent	No action required	Decreased antihypertensive effect of amlodipine	Unknown	UpToDate
Amitriptyline, estradiol	1	Minor	Excellent	Dose adjustments	Possible attenuation of antidepressant effectiveness and tricyclic toxicity	Inhibition of hepatic metabolism of the antidepressant	Micromedex
Phenytoin, losartan	1	Major	Fair	Consider an alternative, monitor losartan decreased effects	Decreased losartan effects (CYP3A4[c] substrate)	CYP3A4[c] inducers may increase the metabolism of CYP3A4[c] Substrates	UpToDate

[a] Central Nervous System
[b] Gamma aminobutyric acid
[c] Cytochrome P450